

## Does Environmental Exposure to Manganese Pose a Health Risk to Healthy Adults?

*Manganese is an essential nutrient that also may be toxic at high concentrations. Subjects chronically exposed to manganese-laden dust in industrial settings develop neuropsychological changes that resemble Parkinson's disease. Manganese has been proposed as an additive to gasoline (as a replacement for the catalytic properties of lead), which has generated increased research interest in the possible deleterious effects of environmental exposure to manganese. Low-level exposure to manganese has been implicated in neurologic changes, decreased learning ability in school-aged children, and increased propensity for violence in adults. However, a thorough review of the literature shows very weak cause-and-effect relationships that do not justify concern about environmental exposure to manganese for most of the North American population.*

Key words: manganese, environment, toxicity, violence, industrial pollution

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Manganese (Mn) is an essential metal nutrient.<sup>1</sup> It is also toxic and toxicity is well documented in humans. Inhalation of Mn-laden dust can cause a Parkinson's like neuromuscular condition<sup>2</sup> that has primarily been described in miners who inhale large amounts daily. Toxicity is not considered a risk to individuals outside of Mn-contaminated industrial settings, and thus environmental overexposure to Mn has not been considered a research priority.

However, the journal *Science* recently featured an article entitled "Manganese: A High-octane Dispute,"<sup>3</sup> which reviewed concerns of the use of methylcyclopentadienyl manganese tricarbonyl (MMT) as a replacement

for lead in gasoline. Canada has approved use of MMT because they believe that the amount of Mn in the atmosphere from MMT in gasoline is insignificant compared with total daily environmental exposure,<sup>4,5</sup> but recent studies suggest that low-level exposure to Mn causes adverse changes in behavior, cognition, and neurologic function. This has led to the hypothesis that, like lead (Pb), there is an incremental risk to increased exposure to Mn that can only be detected at the population level, not at the individual level.<sup>3</sup>

Research that has shown adverse effects from environmental Mn has given rise to much popular concern and activism over the new "lead" in the environment. The World Wide Web lists hundreds of sites devoted to Mn toxicity, including a site<sup>6</sup> that lists Mn-containing foods and provides direct links to attorneys with experience in Mn lawsuits. Other sites, such as the Violence Research Foundation, have the express purpose of demonstrating that environmental toxins, of which Mn is one of the most important, are a major cause of violent crime.<sup>7</sup> The Violence Research Foundation has conducted nutritional supplementation programs in California prisons, and is currently conducting a much larger intervention study with inmates in the Mexico City jail (although these studies have been reported by news organizations, there are no reports in the scientific literature).<sup>7</sup> The general-circulation periodical *Popular Mechanics* (June, 2003, The Chemistry of Violence<sup>8</sup>) featured an article stating that Mn functions as "reverse Prozac," decreasing brain serotonin and increasing propensity for violence. Numerous internet sites have published similar articles.

The hypothesis that Mn exposure causes violent behavior also has been advanced by some academicians. President R. Masters of the Foundation for Neuroscience and Society in the School of Government, Dartmouth College, has published 17 books and 150 research articles; he has proposed that Mn and Pb pollution explain many variations in violent crime rates.<sup>9,10</sup> He hypothesizes that toxic metals cause impulsive and aggressive behavior, that exposure to these metals is high in inner cities, and that criminals are more likely to have been exposed during youth to these chemicals. These hypotheses were developed by comparing crime rates in U.S.

This review was prepared by John W. Finley, Ph.D., United States Department of Agriculture, Agricultural Research Service, Grand Forks Human Nutrition Research Center, Grand Forks, ND 58202, USA. The U.S. Department of Agriculture, Agricultural Research Service, Northern Plains Area, is an equal opportunity/affirmative action employer and all agency services are available without discrimination.

counties that had Environmental Protection Agency (EPA)–documented releases of Mn into the atmosphere (520/100,000; crimes/100,000 population) to counties without documented releases (350/100,000; significant difference,  $P = 0.004$ ).<sup>9</sup> Masters et al.<sup>10</sup> concluded that, after controlling for demographic and socioeconomic variables, Pb and Mn pollution were risk factors for higher rates of violent crime.<sup>9</sup>

Consequently, environmental exposure to Mn has become a political issue. Even though diet is the greatest source of Mn exposure for most people, the nutrition community has had little to add to the discourse, and a thorough review of the available research shows that a vigorous debate is necessary. Certainly metals can alter behavior; a child exposed to Pb has a decreased IQ, although the impact of low-level exposure is minor compared with socio-demographic factors.<sup>11</sup> Other studies report a link between Pb and Attention Deficit–Hyperactivity Disorder (ADHD).<sup>12</sup> There is no doubt that Mn causes behavioral changes at high levels of exposure,<sup>13,14</sup> and a Chinese report indicated that high concentrations of Mn in drinking water were associated with learning disabilities in schoolchildren.<sup>15</sup>

Acute Mn toxicity in humans, often called Mn-induced Parkinsonism, is characterized by progressive neurologic deterioration with bradykinesia, tremor, impaired postural reflexes and dystonia, and elevated whole blood, urine, and fecal Mn.<sup>16</sup> It is believed that  $Mn^{3+}$  bound to transferrin crosses the blood-brain barrier and enters cells by using receptor-mediated endocytosis<sup>17</sup>; magnetic resonance imaging (MRI) has documented Mn accumulation in the human brain of subjects with signs of toxicity.<sup>18</sup> The specific mechanisms of toxicity are unknown but favored theories include oxidation of dopamine<sup>19</sup> and inhibition of mitochondrial and/or synaptic cleft function.<sup>20</sup> Mn retention is controlled in large measure by biliary excretion, and Mn accumulation in the

brain is controlled by the blood-brain barrier; therefore infants, very young children,<sup>21</sup> and adults with liver disease may be more at risk for Mn toxicity.<sup>22</sup> Molecular studies have demonstrated that Fe and Mn may be transported in mammals by a divalent metal transporter (DMT1, DCT1, or Nramp2)<sup>23</sup>; this may explain why Fe deficiency increases Mn absorption and, perhaps, susceptibility to toxicity.<sup>24</sup> The following discussion of possible negative effects of Mn does not apply to these groups, therefore, and is only applicable to healthy adults with adequate Fe status (although it is recognized that people with low Fe status or Fe deficiency may represent a sizable portion of the population).

Regulations regarding Mn exposure have been issued independently both by the EPA and the Occupational Safety and Health Administration (OSHA) (Table 1). In general, oral exposure limits are relatively high (limit of 10,000  $\mu\text{g/day}$ ; average daily intake of Mn from food ranges from 2000 to 9000  $\mu\text{g/d}$ ).<sup>25</sup> Exposure limits for airborne sources of Mn are much lower, with the EPA reference dose set at 0.5  $\mu\text{g Mn/m}^3$ . Airborne concentration limits for industry are generally between 100 and 5000  $\mu\text{g Mn/m}^3$ , depending on the duration. Ambient air concentrations of Mn are 0.01 to 0.03  $\mu\text{g Mn/m}^3$  in non-industrial areas and 0.01 to 0.07  $\mu\text{g/m}^3$  in industrial areas. The daily intake of Mn from the air is 2  $\mu\text{g/day}$  in areas without ferro- or silicomanganese industries, and as high as 10  $\mu\text{g/day}$  in areas with such industries, while some short-duration 24-hour peak emissions have resulted in exposures of 200  $\mu\text{g/day}$  (ambient air Mn concentrations of 0.2 to more than 0.5  $\mu\text{gMn/m}^3$ ).<sup>26</sup>

Oral Mn exposure levels set by the EPA agree with the “no observed adverse effects level” set by the Food and Nutrition board committee for the Institute of Medicine.<sup>27</sup> Both groups have set the upper limit at 10 or 11 mg/day. This upper limit is almost five times the recom-

**Table 1.** Manganese Exposure Limits Set by Various Governmental Agencies

Measure	Definition	Value
EPA R <sub>f</sub> C Environmental Protection Agency, Reference dose, airborne exposure	EPA, max daily intake over a lifetime	0.5 $\mu\text{g Mn/m}^3$
TLV-TWA Threshold Limit Value–Time-Weighted Average	Occupational Safety and Health Administration (OSHA), airborne concentration all workers can be exposed for 40 h	0.2 mg/m <sup>3</sup>
REL-TWA Recommended Exposure Limit–Time-Weighted Average	OSHA, highest allowable airborne concentration in 10-h shift	1 mg Mn/m <sup>3</sup>
PEL-TWA Permissible Exposure Limit–Time-Weighted Average	OSHA, limit that must never be exceeded	5 mg Mn/m <sup>3</sup>
EPA Lowest Observed Adverse Effect Level (LOAEL)	EPA, maximum no effect airborne concentration	150 $\mu\text{g/m}^3$
U.S. EPA Reference dose for oral exposure Adequate Intake (AI)	EPA, maximum oral intake over lifetime Food and Nutrition Board, Institute of Medicine	10 mg/d 2.3 mg/d (men) 1.8 mg/d (women)

mended adequate intake for adult men (2.3 mg/d) or women (1.8 mg/d).

Behavioral and neuropsychologic tests have been used to study physiologic effects of occupational exposure to airborne concentrations of Mn well below those shown to cause acute toxicity; the results of seven studies are summarized in Table 2. These studies were conducted on workers in foundries and alloy production facilities, and residents down-wind of such facilities. Three studies showed clear deleterious effects of Mn exposure,<sup>35–37</sup> one study found no effects,<sup>40</sup> and the others had mixed or questionable findings.<sup>17,38,39,41–43</sup>

Lucchini et al.<sup>31</sup> found that Mn exposure impaired several neurologic functions, but blood Mn concentrations were not associated with exposure. Wennberg et al.<sup>32</sup> reported that Mn exposure resulted in impaired finger tapping and digit span, but not electroencephalography (EEG) measures or psychiatric exams. Gibbs et al.<sup>33</sup> did not find any significant effects of Mn exposure on multiple psychological tests and neurologic measures.

The studies of Mergler et al.<sup>14,34,35</sup> have received much attention. Subjects from southwestern Quebec, who lived downwind of industrial facilities with a history of Mn release, were divided into two groups with blood Mn concentrations greater than or less than 7.5 µg/L. Older men with higher blood Mn had significant disturbances in mood scores.<sup>14</sup> However, the most serious effects on psychological (distress, learning, and recall) and neurologic (coordinated upper limb movements and tremor) measures were in men with high blood Mn who also were heavy consumers of alcohol (>420 g/wk).<sup>35</sup> The authors concluded that Mn neurotoxicity was a continuum of dysfunction with subtle changes at all levels of intake. However, the authors did not justify using 7.5 µg Mn/L blood as a breakpoint for designation of high or low Mn exposure, and most significant effects were two- or three-way interactions, making it difficult to determine the real association. Thus, the mass of this literature still does not give clear indications of the danger of low-level Mn exposure.

There are a few reports of environmental exposure

to sources of Mn other than a Mn-emitting industry. An Australian island with extensive geologic deposits of Mn has been mined since the 1960s, and Mn exposure was blamed for neurologic and behavioral impairment in the indigenous population. Residents not involved in mining had elevated concentrations of Mn in the hair and there are numerous reports of neurologic dysfunction.<sup>36</sup> In reviewing the medical data, however, Kilburn<sup>36</sup> concluded that “available evidence can only implicate manganese by association. . . until then . . . manganese must remain an ‘element of doubt.’ ” Loranger and Zayed<sup>4</sup> used mathematic modeling to predict Mn exposure in the St. Lawrence ecozone (the same general area studied by Mergler et al.) from gasoline-emitted MMT. They showed that more than 99% of total exposure was through food, and the contribution of Mn from MMT was biologically insignificant. Kondakis et al.<sup>37</sup> studied elderly Greek adults (65–68 y) that consumed well water from three sites with Mn concentrations of 0.004 to 0.15, 0.08 to 0.25, and 1.8 to 2.3 mg Mn/L. Compared with non-exposed controls, individuals with higher Mn intakes showed significantly impaired neurologic scores and increased hair Mn concentrations. However Vieregge et al.<sup>38</sup> found no neurologic impairment in subjects that had consumed water that contained more than 0.3 to 2.1 mg Mn/L for more than 40 years. Chinese children exposed to fields with sewage irrigation and high Mn content (0.24–0.35 mg/L, high; 0.03–0.04 mg/L, control) had significantly impaired short-term memory, manual dexterity, and visuo-perceptive speed.<sup>15</sup> The route of Mn exposure was believed to have been through well water, but other sources were not investigated.

Data supporting the hypothesis that Mn exposure can increase violent crime risk also have many weaknesses. Masters<sup>10</sup> analyzed a subset of the data comparing crime rates in areas with and without Mn release. When a t-test was used to compare counties with violent crime rates over 400/100,000 or less than 100/100,000, higher crime rates were significantly associated with more reports of Mn release. However, the associations became more complex when other variables were con-

**Table 2.** Reports of Neuropsychological Impairment of Subjects Exposed to Low Concentrations of Airborne Mn

Study	Subjects	Mn Exposure	Duration	Significant Effects
Iregren <sup>28</sup>	Foundry workers	150 µg/m <sup>3</sup> , air	10 y	Y
Roels et al. <sup>29</sup>	Foundry workers	950 µg/m <sup>3</sup> , air	5.2 y	Y
Mergler et al. <sup>30</sup>	Alloy production workers	230 µg/m <sup>3</sup> , air	14.6 y	Y
Lucchini et al. <sup>31</sup>	Alloy production workers	157–1597 µg/m <sup>3</sup> , air	NA	?
Wennberg et al. <sup>32</sup>	Foundry workers	160–410 µg/m <sup>3</sup> , air	NA	?
Gibbs et al. <sup>33</sup>	Foundry workers	200 µg/m <sup>3</sup> , air	NA	No
Mergler et al. <sup>14,34,35</sup>	Residents down-wind of Mn-emitting industries	Low, but unknown	NA	?

sidered. Similar to Sassine et al.,<sup>35</sup> the Mn effect was strongest in individuals with high alcohol usage ( $P = 0.0001$ ), and when other variables (e.g., socioeconomic factors, alcohol usage) were included in a multiple regression predictive model, Mn and Pb releases were not found to be significant predictors.

Five reports have compared the amount of trace elements in the hair of violent and non-violent offenders in prison populations.<sup>39–43</sup> (Table 3) Only Gottschalk et al.<sup>39</sup> and Schrauzer et al.<sup>40</sup> reported significantly greater Mn concentrations in the hair of violent offenders. Interestingly, the other studies found increases in Pb and Cd, but not Mn, whereas Gottschalk et al.<sup>39</sup> and Schrauzer et al.<sup>40</sup> did not find any increases in these elements. Collectively these studies measured almost 100 variables. The large number of variables in these studies, and the lack of agreement between the ones showing elevated Mn<sup>39,40</sup> and the others<sup>41–43</sup> leave open the possibility that the significant effects of Mn reflect only random statistical variation.

The hypothesized mechanism of neurotoxicity from inhaled Mn is that Mn absorbed from the lungs bypasses first-pass metabolism, goes directly to the brain, and crosses the blood-brain barrier. Based on an average dietary intake of 5000  $\mu\text{g}$  Mn/day, and 4% absorption, 200  $\mu\text{g}$  of Mn/day enters the circulation from food.<sup>44</sup> A person living downwind of a Mn-emitting source may, under extreme conditions, encounter Mn exposures as great as 200  $\mu\text{g}/\text{day}$ .<sup>26</sup> Therefore, assuming 100% retention of the airborne Mn, the total daily Mn exposure would be 200  $\mu\text{g}$  (from diet) plus 200  $\mu\text{g}$  (from air) for a total of 400  $\mu\text{g}/\text{day}$ . The WHO lifetime exposure recommendation (from oral exposure) is 10 mg/day; assuming that 4% is absorbed, 400  $\mu\text{g}$  of Mn/day may safely enter circulation. Therefore, even if an individual lived with the most extreme Mn pollution for 24 hours every day, total Mn exposure would still be within the permissible limit (in fact, most Mn-emitting industries result in exposures of only 10  $\mu\text{g}/\text{d}$ <sup>26</sup>).

Mn exposure from MMT in gasoline poses even less of a risk. Estimates suggest that MMT use in gasoline

would increase Mn exposure to 99% of the population by less than 0.15  $\mu\text{g}/\text{m}^3$ , resulting in a total of only 3  $\mu\text{g}$  of additional Mn absorbed/day.<sup>4</sup>

Dietary studies have demonstrated that intakes of  $>5$  mg Mn/day can be safely tolerated by healthy adults. Davis et al.<sup>45</sup> supplemented women with 15 mg of Mn/day for 124 days (total dietary intake plus supplemental intake of 17 mg/d) and reported only elevated plasma Mn concentrations and lymphocyte MnSOD activities. Urinary Mn, an excretory route that becomes more important at high Mn intakes, was unaffected by treatment. Finley<sup>24</sup> fed women either less than 1 or 9.5 mg Mn/day for 60 days and found that higher Mn intakes were compensated for by decreased absorption and increased excretion. In a follow-up study,<sup>46</sup> subjects were fed  $<1.0$  or 20 mg Mn/day for 60 days in a cross-over design. An extensive battery of psychological tests and neurologic exams was administered before and after dietary periods, and <sup>54</sup>Mn whole-body counting was used to estimate Mn absorption retention and turnover. Measures of Mn status (plasma and lymphocyte Mn) were unaffected by dietary Mn; the efficiency of Mn absorption (%) and biologic half-life were almost twice as great in subjects fed low dietary Mn than in subjects fed high dietary Mn, again demonstrating homeostatic control of Mn retention. As a result, neurologic tests were unaffected by Mn status, and the only psychological variable affected was self confidence (decreased self confidence with high dietary Mn).

The above discussion applies to healthy adults with adequate Fe status. There is evidence, however, that low Fe status may alter Mn homeostasis. Low-Fe diets increase Mn absorption,<sup>47</sup> and Chua and Morgan reported that Fe-deficient diets had increased uptake of Mn into the brain.<sup>48</sup> Iron deficiency in humans also enhances Mn absorption; women in the lowest 10% of serum ferritin concentrations absorbed three- to fivefold more Mn than women in the top 10% of serum ferritin concentrations.<sup>24</sup> Presently, however, there is no direct evidence that women with low Fe status are at increased risk of toxicity from inhaled or oral exposure to moderate concentrations of Mn.

Consequently, a review of the available literature reveals only circumstantial evidence that minor environmental exposure of healthy adults to Mn can have deleterious effects. A notable exception may be women with low Fe status, for whom there is evidence that Mn absorption may be greatly increased.<sup>24</sup> It is well accepted that inhalation of toxic amounts of Mn (e.g.,  $>1.0$  mg/d) can affect neuropsychological function; such knowledge may have caused investigators to see trends and patterns and suggest hypotheses regarding low-level exposure to Mn that simply are not supported by the data.

**Table 3.** Reports of Associations between Trace Element Concentrations in Hair and Propensity for Violent Crime

Study	Metal Concentrations Significantly Elevated in Hair of Violent Criminals
Gottschalk et al. <sup>39</sup>	Mn
Schrauzer et al. <sup>40</sup>	Mn, Li decreased
Pihl and Ervin <sup>41</sup>	Pb, Cd
Marlowe et al. <sup>42</sup>	Pb, Cd, Hg, Si; Li decreased
Schauss et al. <sup>43</sup>	Pb, Cd, Cu; Mn non-significantly decreased



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## Beverage Consumption and Risk of Obesity among Native Americans in Arizona

*Native Americans face some of the highest rates of obesity and diabetes in the world. Despite numerous education programs to reduce obesity among Native Americans, little attention has been paid to reducing fructose, particularly in the form of high-fructose corn syrup in beverages. Considerable data indicate that energy from beverages does not displace energy from other foods throughout the day, often leading to energy imbalance, and numerous studies have documented that beverages are a leading contributor to energy intakes among Native Americans. Prevention programs that target pregnant women and parents of infants and very young children are necessary to halt the epidemic of obesity among Native Americans; one approach may be by promoting sugar-free beverages.*

**Key words:** Native American, beverage, energy, obesity

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This review was prepared by Christopher M. Wharton, M.S., and Jeffrey S Hampl, Ph.D., R.D., Department of Nutrition, Arizona State University, 7001 E. Williams Field Rd., Mesa, AZ 85212, USA. This project was supported with funding provided by The Cooperative State Research, Education, and Extension Service of the U.S. Department of Agriculture (03-35200-13445).

Across all age groups and ethnicities, the well-recognized epidemics of overweight and obesity grow worse with each passing year. The majority of adults in the United States (~64.5%) are overweight or obese based on body mass index (BMI, kg/m<sup>2</sup>), and between 10 and 15% of U.S. children are overweight.<sup>1,2</sup> Preventing and treating overweight and obesity are high priorities because these conditions are associated with an increased risk for chronic diseases, including cardiovascular disease, diabetes, hypertension, pulmonary stress, and orthopedic problems.<sup>3–8</sup>

Native Americans particularly suffer from obesity and related health issues, beginning very early in life.<sup>4</sup> Recent data from the Pathways Study (*n* = 1704) showed that 30.5% of girls and 26.8% of boys were greater than the 95th percentiles for BMI-for-age (i.e., overweight); 21.0% of girls and 19.6% of boys had a BMI-for-age that was ≥85th and <95th percentiles (i.e., at risk for overweight).<sup>9</sup> The proportion of Native American children with a BMI-for-age ≥85th percentile was consistently higher than national averages in all of the communities studied. For example, based on recent data from the National Health and Nutrition Examination Survey (NHANES), 11% of 6- to 11-year-olds across the country have a BMI-for-age that is greater than the 95th percentile, compared with 28.6% of Native American children of the same age in the Pathways study.<sup>9</sup>

Based on research conducted in Arizona, obesity appears to begin very early in life among Native Amer-